

HIERARCHICAL NEUROPSYCHOLOGICAL FUNCTIONING AMONG PEDIATRIC
SURVIVORS OF ACUTE LYMPHOBLASTIC LEUKEMIA

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Acute lymphocytic leukemia (ALL) is one of the most common types of pediatric cancers. Improvements in treatment within the last 20 years have resulted in reduced mortality and a greater focus upon quality of life. Several researchers have documented neuropsychological impairments in children following treatment for ALL; however, there have not been any comparative studies documenting differences in neuropsychological functioning based upon treatment modality despite the documented effects of radiation therapy and combined radiation/chemotherapy upon the developing brain. In addition, past studies have focused on unitary measures, ignoring the hierarchical relationship between basic cognitive functions and more abstract skills. This study examined the neuropsychological functioning of 81 children who were treated for ALL at a metropolitan children's hospital. All children were tested a minimum of two years after the final treatment session and were administered the NEPSY. Results do not support any interactions or main effects with the exception of the age of the child at diagnosis. Children diagnosed prior to the age of 5 showed greater impairments on tasks measuring attention, memory, and visuospatial reasoning in comparison to peers diagnosed after age 6.

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CHAPTER 1: INTRODUCTION

HIERCHICAL NEUROPSYCHOLOGICAL FUNCTIONING AMONG PEDIATRIC SURVIVORS OF ACUTE LYMPHOCYTIC LEUKEMIA

Within the last 50 years, medical science has progressed at a rate unsurpassed by any other time era. Many diseases once considered incurable, such as cancer, are being treated with remarkable results and in many cases, remit. Whereas in the 1970's childhood cancers such as acute lymphocytic leukemia (ALL) had a survival rate of less than 60% (National Cancer Institute, 2005b), epidemiological reports indicate that more than 87% of children afflicted with this illness achieved complete remission and were living normal lives in 2001 (2005b).

However, because treatment often entails cranial irradiation therapy and intrathecal injection of chemotherapeutic agents into the central nervous system during a critical period of development, concerns regarding the long-term effects of treatment for ALL remain a significant concern (Moleski, 2000; Said, Waters, Cousens, & Stevens, 1989). Due to the high percentage of children who are enrolled in special education following treatment for ALL (Brown & Madan-Swain, 1993), research has primarily focused on cognitive functioning in these children. Beginning in the late 1970's, studies have attempted to determine if standard treatment modalities result in decrements in overall intellectual ability, attention, and psychological adjustment. However, fewer studies have examined specific cognitive domains such as memory, sensorimotor abilities, and visuospatial skills (Butler & Copeland, 1993).

The long-term cognitive consequences of ALL have been further obscured by problems with research methodology and complex interactions among multiple variables (Brown & Madan-Swain, 1993; Butler & Copeland, 1993). At the present time, research suggests a pattern of six obstacles: variations in treatment protocols, the age and gender of child at diagnosis, latency between final treatment session and neurocognitive evaluation, use of appropriate comparison groups, measurement of neuropsychological functioning in pediatric populations, and a tendency to treat the various subcomponents of neuropsychological functioning as isolated processes that operate independent of one another. It is the intent of this study to delineate how each of these factors, both as individual variables and in combination with one another, help explain the variability in research findings regarding neuropsychological functioning among pediatric ALL survivors.

Variations in Treatment Protocol

For both ethical and practical reasons, it is impossible to study life-threatening illnesses such as cancer via experimental design; ALL cannot be induced experimentally nor can researchers randomly assign patients to different treatment groups. Consequently, the majority of research to date has been retrospective. While a valuable tool in studying chronic or life-threatening illnesses, retrospective studies are fraught with a number of methodological problems (Stehbens et al., 1994). Perhaps of greatest concern within the area of cancer research is that few studies control for the specific type of treatment (Butler & Copeland, 1993; Moleski, 2000). The long-term effects of radiation may differ from those caused by intrathecal chemotherapy alone or in combination with other treatments (Butler & Copeland, 1993; MacLean et al., 1995;

Moleski, 2000; Stehbens et al., 1994). Studies conducted in the late 1980's have demonstrated the deleterious effects of irradiation upon the developing brain (Moleski, 2000; Stehbens et al., 1994). Brown & Madan-Swain (1993) note that children who had been treated with radiation scored significantly lower than their healthy siblings on measures of overall intellectual functioning, visuospatial abilities, and verbal memory. This is consistent with other studies which have examined the specific effects of central nervous system irradiation and suggest a pattern of impairments on neuropsychological measures (Cousens et al., 1988; Moleski, 2000; Said, Waters, Cousens, & Stevens, 1989). Even among the studies which have focused exclusively on radiation treatment, differences in the amount of radiation administered, length of treatment session, and frequency or intensity of radiation treatments have rarely been addressed (Brown & Madan-Swain, 1993; Butler & Copeland, 1993; Moleski, 2000).

In comparison, intrathecal chemotherapy has been linked with similar impairments in neurocognitive performance, although to a much milder extent (MacLean et al., 1995; Moleski, 2000; National Cancer Institute, 2005a; Regan & Reeb, 1998). Because methotrexate (MTX) is the most commonly prescribed chemotherapeutic agent (Armstrong & Horn, 1995; Johnston, 1985; Mauer et al., 1993; Précourt et al., 2002; Stehbens et al., 1991) comparisons among children who have received intrathecal chemotherapy only are much easier and therefore, have greater heuristic value. However, problems still exist as few studies provide information regarding drug titration, treatment intensity (e.g. chemotherapy administered within a short time span versus over long period of time), and time intervals between each treatment session. Research

has shown that more intensive treatment sessions or higher doses of chemotherapy often result in more severe impairments (Copeland, 1996; Moleski, 2000).

Past research demonstrates that neurocognitive impairments are most apparent in children who receive a combined treatment regimen consisting of both radiation and intrathecal methotrexate (Brown & Madan-Swain, 1993; MacLean et al., 1995; Moleski, 2000; National Cancer Institute, 2005a; Stehbens et al., 1994). MacLean et al. (1995) notes that children who received the combined treatment performed significantly worse on the McCarthy Motor Scale and Token Test. A study conducted by Moleski (2000) found impairments in memory, metacognition, visuomotor skills, processing speed, and visuospatial abilities. Although Stehbens et al. (1994) failed to find any significant differences in cognitive performance when comparing children who received either combined radiation/intrathecal or intrathecal treatment only, it should be noted that all subjects were tested within the first 9 months after their last treatment. Due to the sequence of brain development, neurobehavioral alterations may not be evident until a later time (Brouwers et al., 1985; Fletcher & Copeland, 1988).

Age and Gender of Child at Initial Diagnosis

Another factor which likely influences performance on neuropsychological measures is the age at which the child was first diagnosed and treated. While a specific age has not been determined, studies indicate that young children under the age of 5 typically manifest a greater number and more severe cognitive difficulties (Brown & Madan-Swain, 1993; Moleski, 2000; Regan & Reeb, 1998; Stehbens et al., 1994). According to a study conducted by Said et al. (1989), age at diagnosis correlated with lower full scale IQ (FSIQ), verbal IQ (VIQ), and perceptual reasoning abilities (PIQ) as

measured by the Kaufman Brief Intelligence Test (K-BIT); the younger the child was at diagnosis, the poorer the performance. This concurs with the findings of several other studies (e.g. Brown & Madan-Swain, 1993; Ciesielski et al., 1999; Moleski, 2000; Stehbens et al., 1994) which have linked young age at diagnosis with greater neuropsychological impairments over time.

However, the negative effects of irradiation or chemotherapy during the first 5 years of life may be mediated by type of treatment (Brown & Madan-Swain, 1993; Moleksi, 2000; National Cancer Institute, 2005a; Regan & Reeb, 1998). According to Armstrong and Horn (1995), children who received radiation therapy showed greater deficits in non-verbal skills in comparison to intact language abilities and abstract reasoning skills; however, only children who had been treated prior to the age of 5 exhibited severe, pervasive impairments. There was a positive, linear correlation between age at diagnosis and perceptual motor skills among all children, including those who had received radiation (Regan & Reeb, 1998). Although no studies to date have directly compared the performance of children who received only intrathecal chemotherapy or radiation for the purpose of delineating cognitive impairments attributable to radiation versus chemotherapy, Brown & Madan-Swain (1993) note that age is only predictive of neurocognitive performance among children who receive radiation.

Past research has alluded to the importance of gender in predicting long-term outcome. Several authors (e.g. Brown & Madan-Swain, 1993; Mulhern, 1994; Smith et al., 2005) have demonstrated that female ALL survivors evidence greater decrements and more global impairments on neuropsychological measurements in comparison to

their male counterparts. This finding is surprising considering that males outnumber females 4:1 and 3:1 in the number of children diagnosed with a learning disability and ADHD, respectively (APA, 2002; CHADD, 2000). Both of these diagnoses have been linked with neuropsychological impairments and thus, it seems unusual that male ALL survivors would obtain higher scores in comparison to their female counterparts.

As with age, a critical factor in understanding how female gender and neurocognitive performance interact may be related to treatment modality (Mulhern, 1994). Copeland et al. (1996) proposes that gender differences on neurocognitive measures are only evident when radiation is a component of treatment. In a study examining the effects of intrathecal methotrexate upon cognitive abilities, females did not evidence any clinically significant differences on measures of global intellectual ability in comparison to their male counterparts (Copeland, 1996). Mulhern (1994) reports similar results but notes that when chemotherapy was combined with radiation, females performed worse on measures of perceptual abilities and overall cognitive functioning. Furthermore, females showed significantly greater declines in verbal skills following a brief delay; these effects were more pronounced with higher levels of radiation (Mulhern, 1994). Although no direct comparisons between females receiving irradiation alone versus combined radiation/ chemotherapy have been performed, Copeland et al. (1996) hypothesizes that the combined treatment results in a synergistic effect, augmenting the deleterious effect of each individual agent upon cognitive functioning. Ironically, researchers (e.g. Butler & Mulhern, 2005; Smith et al., 2005) note that while female gender is associated with greater vulnerability to cognitive deficits following treatment for ALL, it is also a factor linked with a more favorable prognosis.

Latency Between Diagnosis and Neuropsychological Evaluation

Because both radiation and intrathecal chemotherapy are intended to systemically destroy all cancerous cells, brain structures which play a key role in higher order cognitive functioning may be damaged or altered (Brouwers et al., 1985; Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Schatz, Kramer, Ablin, & Mathhay, 2000; Stehbens et al., 1994). Evidence of damage to this area may not become evident until later in a child's life (Brown & Madan-Swain, 1993; Packer et al., 1987; Schatz et al., 2000; Stehbens et al., 1994). The length of time between the final treatment session and neuropsychological testing thus becomes an important variable. Although recent studies have begun to take this factor into consideration, earlier research was clouded by the fact that children who were less than 1 year post treatment were being compared to those who were tested several months or years after the final treatment session (Brouwers et al., 1985; Stehbens et al., 1994). Fletcher and Copeland (1988, pp. 503) posit that "the majority of studies conducted within 1 year of diagnosis show no [neurocognitive] effects, but those with a latency of 3 or more years do show a significant effect." In fact, among a group of 17 pediatric ALL survivors tested six years after diagnosis, nearly 96% evidenced impairments on neuropsychological measures with the greatest deficits noted in perceptual-motor and sensory tasks (Fletcher & Copeland, 1988). Several authors (e.g. Brouwers et al., 1985; Moleski, 2000; Packer et al., 1987; Regan & Reeb, 1998; Schatz et al., 2000) note that while impairments in neurocognitive functioning are not usually detectable until 2-3 years after treatment; Brouwers et al. (1985) maintains that deficits may not become apparent until up to 7 years later. According to Brown and Madan-Swain (1993), a child's brain does not reach

full maturity until the second decade of life and thus, the longer the latency between the child's age at diagnosis and chronological age, the more pervasive and severe impairments in neuropsychological functioning may become.

Appropriate Comparison Groups

Determining the presence and severity of neuropsychological deficits is further compounded by a lack of appropriate comparison groups (Brown & Madan-Swain, 1993; Giralt et al., 1992; Liu et al., 1996; Moleski, 2000; Regan & Reeb, 1998; Schatz et al., 2000). To control for all individual factors which might influence performance on neurocognitive measures, a child should ideally be tested prior to beginning treatment for ALL and then be re-evaluated periodically to monitor changes. Alternatively, a true experimental design would entail a control group of same age, sex-matched children who received a placebo treatment. Obviously this design could never be implemented as it is highly unethical to withhold treatment for a child with a life-threatening illness solely for research purposes. However, in order to truly discern the individual contributions of psychosocial, personality, and treatment factors upon cognitive functioning, one cannot rely upon retrospective studies (Stehbens et al., 1994).

Thus, in an effort to control for factors such as genetics, pre-existing medical conditions or brain damage, history of head injuries, and other environmental influences while continuing to provide children with the treatment they need, several authors (e.g. Brown & Madan-Swain, 1993; Kaemingk et al., 2000; Moleski, 2000; Murdoch & Boon, 1999; Regan & Reeb, 1998; Taylor, 1997) have used healthy siblings as a basis for comparison. Said et al. (1989) note that in comparison to same age siblings, ALL survivors evidenced poorer nonverbal reasoning skills, resulting in a lower full scale and

performance IQ scores as measured by the WISC-IV. This corroborates the findings of Moss, Nannis, and Poplack (1981) and Twaddle, Britton, Craft, Noble, and Kernahan (1983) who both noted that the greatest discrepancies were found on the Information, Similarities, Arithmetic, Comprehension, Picture Completion, Picture Arrangement, and Block Design subscales of the WISC-IV. Performance on these measures has been associated with higher level cognitive functions such as working memory, visual attention, spatial and sequential reasoning, and remote memory (Moss et al., 1981; Sattler, 1992).

However, the validity of these results must be interpreted with caution as there is some evidence that the intellectual ability of ALL siblings may not be normally distributed (Giralt et al., 1992; Jannoun, 1983; Moss et al., 1981; Twaddle et al., 1983). Giralt et al. (1992) notes that the mean IQ for healthy siblings is 112-113. According to Moss et al. (1981), the mean full-scale IQ for ALL survivors ranges from 98.6 to 99.9, whereas their healthy siblings obtained scores of 110-116. Twaddle et al. (1983) applied a correction formula to account for genetic variations based upon an earlier finding that siblings' intellectual abilities generally correlate at a 0.5 level. Results were consistent with other studies which note significantly higher full-scale IQ abilities among healthy siblings in comparison to children who have been diagnosed with ALL (Twaddle et al., 1983). Furthermore, this discrepancy was evident prior to the ALL group receiving any type of treatment (1983).

Measurement of Neuropsychological Functioning in Pediatric Populations

One criticism of past research is an over reliance upon measures not intended for use as neuropsychological instruments. Research is replete with studies that have used measures of global intellectual ability to gauge alterations in memory, attention, and language despite the instruments' insensitivity to neuropsychological processes (Butler & Copeland, 1993; Eiser, 1992; Précourt et al., 2002; Regan & Reeb, 1998). This practice is likely to lead to an increased probability of a type II error in which a significant finding is not identified (Butler & Copeland, 1993). While several studies (e.g. Brown & Madan-Swain, 1993; Espy et al., 2001; Stehbens et al., 1994) allude to the benefit of using a WISC-IV or Kaufman scale as an index of higher order cognitive abilities, research suggests that neurodevelopmental changes following treatment for ALL are subtle and thus, undetectable by instruments which were not intended to assess all of the underlying processes (Butler & Copeland, 1993; Moleski, 2000; Regan & Reeb, 1998). Butler and Copeland (1993, pp. 326-327) point out

Intelligence and achievement tests are not...neuropsychological measures. They were not developed to assess brain-behavior relationships in children; Rather, intelligence and achievement tests were originally developed to predict and assess performance in school

The use of intellectual tests also blurs the distinction between individual neurocognitive processes, rendering it very difficult, if not impossible, to pinpoint specific neuropsychological deficits (Godber, Anderson, & Bell, 2000; Précourt et al., 2002; Regan & Reeb, 1998). Most tasks on intellectual measures entail simultaneous use of different skills (Butler & Copeland, 1993; Eiser, 1992; Moleski, 2000; Reeb & Regan, 1998). For instance, poor performance on the Maze subtest of the WISC-IV may be

attributable to impairments in fine motor skills, visuospatial abilities, ocular tracking, impulsivity, slow processing speed, or any combination of the above. Thus, conclusions regarding neuropsychological functioning which are based upon the results of an IQ test are likely neither reflective of a child's true abilities nor predictive of performance among other ALL survivors.

Another oft-used practice is to try to predict comparisons with same-age peers beyond the tests' normative sample. Because the field of neuropsychology is relatively young and the majority of research stems from work with brain-injured adults, instruments designed to measure neurocognitive abilities in children and adolescents are sparse. There is a tendency to "project downward" or assume that cognitive development is a linear process in which skills are attained in increments of months or years (Dean, 2005; Korkman, Kirk, & Kemp, 1998). For instance, Stehbens (1994) notes that the norms for adolescents 14 years old or older on the Rey Auditory Verbal Learning Test (RAVLT) are all less than one standard deviation, which results in a score that overestimates the degree of neurological impairment. Furthermore, Dean (2005) adds that although efforts have been made to modify the tasks of Halstead-Reitan Test Battery for use with pediatric populations, the child version is essentially the same as the original; thus, the Halstead-Reitan Test Battery for Children is "but a downward revision of the adult battery" (p. 2).

Finally, past studies have relied almost exclusively on measures not intended for use as neuropsychological instruments or those not specifically designed for children (Dean, 2005; Korkman et al., 1998). The Halstead-Reitan Neuropsychological Battery (HRNB), provides an index of neuropsychological impairment based on a 4 point rating

scale (1= average, 2=one standard deviation below the mean, 3= two standard deviations below the mean, and 4=three standard deviations below the mean) but fails to provide information concerning specific areas of cognitive strength or weakness (Dean, 2005; Hebben & Milberg, 2002). Furthermore, the intent of the HRNB is not to tease out specific areas of neuropsychological impairment, but to differentiate 1) organic neurological dysfunction from normal populations, 2) organic neuropsychological dysfunction from specific psychiatric populations, 3) focal from diffuse brain damage, and 4) regional focal dysfunctions in various zones of the brain (Dean, 2005). Information concerning norms and standardization are not provided and thus, transformation of raw data into standardized scores that provide a basis for individual comparisons is impossible (Dean, 2005). The HRNB is founded upon the theory that all brain regions are equally responsible for cognitive functions; thus, skills cannot be localized to specific areas, necessitating administration of the entire test battery in order to determine areas of deficits (Dean, 2005; Hebben & Milberg, 2002). As a result, children may quickly lose interest in the materials or become too fatigued to complete the entire battery to the best of their ability (2002).

In comparison, the Luria-Nebraska is efficacious in assessing levels of neuropsychological dysfunction, but has been criticized for being insensitive to language impairments (2002). Presently, neither the Halstead-Reitan nor the Luria-Nebraska neuropsychological batteries provide norms for children younger than 8 and 6 years of age, respectively (2002). As Stehbens (1994, p.) points out, "it is notable that few neuropsychological instruments have been normed on pre-school age children, a

group that has been identified as being at the greatest risk for neurocognitive impairment.”

Neuropsychological Functioning as Hierarchical Model

In an effort to pinpoint specific underlying neurocognitive deficits which influence more complex processes, the use of a hierarchical model in which basic skills are evaluated prior to testing higher order functions is recommended (Lockwood, Bell, & Colegrove, 1999). Just as it is necessary to rule out more simple diagnoses for a patient who complains of chest pain prior to conducting open-heart surgery, a clinician would be remiss in identifying deficits in complex cognitive processes without first addressing base skills. Thus, before impairments in memory or language can be determined, it is important to first evaluate sensory (i.e. hearing, vision) and attentional processes (Lockwood, Bell, & Colegrove, 1999). This notion of hierarchical cognitive functioning was first proposed by Aleksandr Luria in 1966 (Hebben & Milberg, 2002). Luria maintained that complex cognitive skills are comprised of elementary building blocks that function as lower-level cognitive processes (2002).

To date, most studies have assessed the various components of cognition as unitary processes that operate independent of each other. Past literature suggests that among studies which have attempted to measure both intellectual ability and other cognitive functions such as memory or visuospatial skills, most have examined these factors in isolation of each other, as if processes such as attention and memory operate independent of one another. Results of cognitive batteries and brain imaging studies suggest otherwise, however. Ciesielski et al. (1999, pp. 447) explains:

Functional anatomic studies clearly indicate that multiple brain regions can be activated by memory and learning tasks and may participate in neural processing to different degrees; thus, performance on a memory task may not only be a function of memory, but of additional cognitive and neuroanatomical components such as attentional, visuoperceptual, and motor abilities.

Subsequently, past studies which have employed a piece-meal approach in which inter-related cognitive functions are treated as distinct entities independent of each other likely mask the true nature and complexity of cognitive impairments.

Pathogenesis of Acute Lymphocytic leukemia.

ALL occurs when the bone marrow begins to produce abnormal cells at an uncontrolled rate (Rubnitz & Look, 2000). Many different blood cells originate in the bone marrow & then differentiate into specialized cells such as erythrocytes (red blood cells) and lymphoblasts (white cells) after migration to other parts of the body (Guyton & Hall, 1996). Normally, the body maintains a strict balance of each kind of blood cell so that no one specific type overwhelms the others. In ALL, the cells responsible for cell-mediated and humoral immunity, the lymphocytes, grow uncontrolled, causing normal, healthy cells to be crowded out (Rubnitz & Look, 2000). Diminished red cell levels result in fatigue and pallor while decreased numbers of healthy white cells interfere with the body's ability to ward off infection and recover from injury (National Marrow Donor Program, 2005). As the most common childhood cancer, ALL accounts for more than 31% of newly diagnosed cancers every year (Smith, Ries, Gurney, & Ross, 2005). It is typically diagnosed between the ages of 2-3 years although it can occur in infancy and adulthood (Center for Disease Control, 2005; Smith et al., 2005). The male to female ratio is 2:1; however, females are more likely to experience central nervous system late effects (Berg, Steuber, & Poplack, 2000; Espy et al., 2001). As recent as the 1960's,

ALL was largely untreatable, claiming the lives of nearly 2000 children annually (National Cancer Institute, 2005b). However, with the advent of radiation therapy and chemotherapeutic agents which eliminate cancerous cells throughout the entire body, the survival rate has increased to nearly 90% (National Cancer Institute, 2005b).

Because the cancer cells are interspersed with other cellular components of blood, there is a possibility that cancerous cells will be carried to the brain and tissue of the central nervous system (Moleski, 2000; National Marrow Donor Program, 2005). The brain normally forms a barrier, preventing toxic agents from infiltrating the central nervous system; subsequently, chemotherapeutic drugs are unable to cross from the blood to the brain and cancer cells may proliferate (Berg et al., 2000). Therefore, it is sometimes necessary to augment chemotherapy with radiation to completely rid the body of all cancerous cells (Berg et al., 2000; Moleski, 2000). Research suggests that a failure to provide systemic therapy may greatly increase the risk of relapse (Berg et al., 2000; Moleski, 2000).

Presently, the most common form of treatment for ALL is intrathecal chemotherapy typically using methotrexate combined with one or more of the following: vincristine, asparaginase, prednisone, and cyclosporine (Ghalie et al., 1990; Johnston, 1985; Mauer, 1983; Memon et al., 1995; Menegaux et al., 1994; Nussbaum et al., 1995; Silverman, Sallen, & Cohen, 2000). Because few agents are able to cross the blood-brain barrier on their own, methotrexate must be injected directly into the spine to facilitate the destruction of cancer cells which have migrated into the central nervous system (Dufner et al., 1984; Mauer, 1983; Précourt et al., 2002). However, because methotrexate does not show a greater affinity for the cancerous cells, healthy cells are

often destroyed in the process as well (Armstrong & Horn, 1995; Menegaux et al., 1988; Mulhern, 1994). This results in an increased risk for encephalopathies, seizures, cortical blindness, poor motor control, and difficulties with attention as well as memory, (Armstrong & Horn, 1995; Ghalie et al., 1990; Johnston, 1985; Mauer, 1983; Memon et al., 1995; Menegaux et al., 1994; Mulhern, 1994; Nussbaum et al., 1995; Silverman et al., 2000). Over an extended period of time, brain cells may be permanently damaged, resulting in an increased risk of impairments in neurocognitive functioning (Armstrong & Horn, 1995; Ghalie et al., 1990; Johnston, 1985; Mauer, 1983; Memon et al., 1995; Menegaux et al., 1994; Mulhern, 1994; Nussbaum et al., 1995; Silverman et al., 2000).

While cranial radiation is a less favorable treatment option as a result of its deleterious effects on the developing brain (Dufner et al., 1984; Johnston, 1985; Packer et al., 1987), it is sometimes used in conjunction with intrathecal chemotherapy in cases where there is extensive infiltration of the central nervous system or a high risk of relapse (Moleski, 2000). It has been postulated that the combination of intrathecal methotrexate and cranial irradiation creates a synergistic effect, augmenting the destruction of both cancerous and healthy cells to a degree much greater than what would be expected if each of these agents are used in isolation (Dufner et al., 1984; Frutiger, Fennell, & Parsons, 1999; Johnston, 1985; MacLean et al., 1995; Mauer, 1983; Schatz et al., 2000; Stehbens et al., 1991). Research indicates that methotrexate, as well as other chemotherapeutic agents, lowers the blood-brain barrier threshold, intensifying the effects of radiation (Copeland, 1996; Dufner et al., 1984; Mauer, 1983; National Cancer Institute, 2005a).

Structural Alterations as a Result of Radiation and Intrathecal Chemotherapy

Autopsies suggest that the cumulative effect of chemotherapy, irradiation, or any combination of the two is structural brain damage (Moleski, 2000; Reeb & Regan, 1998; Stehbens et al., 1994;). It is this damage that underlies the purported alterations in attention, memory, verbal skills, and nonverbal reasoning abilities in ALL survivors (Brown & Madan-Swain, 1993; Moleski, 2000; Reeb & Regan, 1998; Stehbens et al., 1994). Functional MRI's and brain dissections support 3 primary areas of structural damage: demyelination, cortical atrophy, and calcifications in gray matter (Frutiger, Fennell, & Parsons, 1999; MacLean et al., 1995; Moleski, 2000; Stehbens et al., 1991; Stehbens et al., 1994).

Beginning in early childhood, the body begins the process of coating nerve cells with a fatty sheath, known as myelin or white matter. This sheath serves several functions including increased speed of neural transmission and rapid repolarization (Guyton & Hall, 1996). Unlike other brain structures, which are typically intact by the age of 4 (Brown & Madan-Swain, 1993), myelinization continues throughout childhood and into early adulthood (Brown & Madan-Swain, 1993; Stehbens et al., 1994). Both chemotherapy and cranial irradiation have been shown to disrupt this process (Fletcher & Copeland, 1988; Moleski, 2000; Reeb & Regan, 1998; Schatz et al., 2000; Stehbens et al., 1994). According to Packer et al. (1987), methotrexate in particular inhibits the formation of a key lipid involved in myelin formation. Because the basal ganglia and frontal lobe extensions are the areas undergoing the most intense myelinization during childhood, neuropsychological impairments are likely to be the most pronounced on measures associated with fine motor skills, attention, executive functions, verbal

memory, and mathematic abilities (Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Moleski, 2000; Reeb & Regan, 1998).

Although ALL survivors do not evidence the same pattern of neurocognitive deficits, which would suggest diffuse damage, researchers have noted that most impairments are concentrated in the right hemisphere (Brown & Madan-Swain, 1993; Reeb & Regan, 1998; Stehbins et al., 1994). This is consistent with findings of decreased white matter as several authors (e.g. Goldberg & Costa, 1981; Kaemingk et al., 2004) note that there is proportionately more white matter in the right hemisphere in comparison to the left hemisphere. A reduction in white matter has been linked with *nonverbal* impairments such as inattention, poor auditory memory, decreased processing speed, and visuospatial abilities (Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Reeb & Regan, 1998; Stehbins et al., 1994).

Cushioned beneath the insulating layers of the myelin sheath, the cerebral cortex contains the brain structures that govern sensory and motor functioning, information processing, memory, organizational/ planning abilities, emotions, and homeostasis of the body (Lezak, Howieson, & Loring, 2004). Within the cranium is also four fluid-filled cavities known as ventricles; these ventricles help maintain the shape of the cerebral cortex by expanding or shrinking according to tissue volume (Lezak et al., 2004). Thus, when brain tissue deteriorates or dies, the ventricles expand via an influx of cerebrospinal fluid (2004). Post mortem examinations of the brains of children afflicted with ALL reveals enlargements in the 4th ventricle, suggesting cortical atrophy (Lezak et al., 2004; Moleski, 2000). In a study conducted by Moleski (2000), nearly 80% of cortical atrophy was attributable to intrathecal administration of methotrexate. Paakko et al.

(1996) found that while white matter changes were found in only a small (10%) proportion of children who were being treated for ALL with a combined radiation/intrathecal methotrexate regimen, 72% of the children showed enlargement of the ventricles and cortical sulci following administration of intrathecal methotrexate. According to Quinn et al. (1997), methotrexate increases homocysteine levels, which causes damage to vascular endothelium and thereby causes subsequent cortical atrophy.

While the precise mechanism of structural damage following treatment for ALL is unknown, Packer et al. (1987) proposes that radiation can cause alterations via three pathways. At the very minimum, radiation causes damage to capillary endothelial cells, resulting in mutation (1987). Ultimately these mutations may result in decreased capillary wall permeability and subsequent decreases in vascularization (National Cancer Institute, 2005a) which leads to cellular necrosis (1987). Second, radiation damages both glial and oligodroglial cells, causing disruptions in the formation of myelin (1987). Finally, Packer et al. (1987) proposes that the damage to the above cells results in the release of antigens, activating an immunological response.

Psychosocial Influences

The neuropsychological impairments brought about by treatment for ALL appear to be further mitigated by several psychosocial variables. Given the present disparities between the affluent and the poor in healthcare coverage and subsequent access to the most technologically advanced treatment facilities, it does not come as a surprise that both socioeconomic status and parental education level influence neuropsychological performance in ALL survivors (Espy et al., 2001; Heaton, Grant, & Mathews as cited in

Butler & Copeland, 1993; Said et al., 1989). According to Trautmann et al. (1988), parental socioeconomic status exceeds all other factors in predicting overall intellectual abilities. This is consistent with earlier studies of environmental influences upon intellectual development which emphasize the link between higher parental education level and increased income, which is typically associated with an enriched learning environment (Turner, Lewis, & King, 2003). Said et al. (1989) note that *paternal* education level, specifically, accounts for a significant amount of variance on the Arithmetic, Vocabulary, Digit Span, Picture Arrangement, Block Design, and Coding subtests of the WISC-IV as well as measures of reading comprehension and word recognition. Espy et al. (2001) adds that *maternal* education level also reliably predicts performance on the Arithmetic subtest of the WISC-IV 4 years post-diagnosis: for every year of maternal formal education beyond high school, a child's score increases by 2.54 points.

Neuropsychological Domains Affected by Treatment for ALL

Sensorimotor Skills

With the exception of one study completed in the late 1980's by Copeland et al. (1988), few studies have specifically addressed the impact of intrathecal chemotherapy and radiation upon sensorimotor functioning. This is surprising given that the basal ganglia, a structure believed to play a pivotal role in both gross and fine motor movements, is one of the areas most affected by chemotherapy and radiation. Copeland et al. (1988) reports that children who received triple intrathecal chemotherapy (methotrexate combined with cytosine arabinoside, hydrocortisone, systemic steroids) or intravenous methotrexate performed significantly worse on

measures of fine-motor skill integration (e.g Finger Tapping, Grooved Pegboard, Trails A & B) and tactile-perceptual abilities one year after diagnosis. In fact, Rourke (1987) asserts that due to the underlying cause of fine-motor skill and tactile-perceptual skills, sensorimotor abilities should be the target of early intervention aimed at teaching the child compensatory behaviors prior to destruction of white matter.

Attention

One of the most frequently reported long-term impairments stemming from treatment for ALL is attentional difficulties (Anderson et al., 1997; Armstrong, Blumberg, & Toledano, 1999; Brown & Madan-Swain, 1993; Ciesielski et al., 1999; Heukrot et al., 1988; Inati et al., 1983; Lesnik et al., 1998; Lockwood et al., 1999; Précourt et al., 2002). Preliminary studies relied upon single measures of attention, thereby yielding equivocal results. It has only been within the last ten years that researchers have begun to accept a multidimensional attention model. Cohen (1993) asserts that since various components of attention overlap with different sensory systems (e.g. vision, hearing, movement), it is imperative that a unitary measure of attention not be used to represent the different facets. He further notes that standardized intelligence tests are insufficient in assessing attention as the aforementioned is a measure of *cognitive* capacity, not attentional capacity. Lezak (2004, pp. 22-23) asserts, “attentional functions differ from [cognitive] functions...in that they underlie, and in a sense, energize the activity of the cognitive functions.”

Thus, it is important to differentiate among the different types of attention (Lezak et al., 2004; Lockwood et al., 1999; Van Zomeren & Brouwer, 1994). Van Zomeren and Brouwer (1994) define *selective attention* as the process of focusing on one set of

stimuli while ignoring other sources of sensory information. *Divided attention*, on the other hand, refers to the ability to attend to two or more sensory inputs simultaneously such as taking notes during a lecture while visually scanning a textbook (1994).

Sustained attention requires the capacity to focus on one source of information for a prolonged period of time and *alternating attention* relates to being able to switch from one information source to another in a continuous fashion (1994). All four types of attention require different skills and provide valuable information concerning cognitive functioning.

Memory

Because attention is a prerequisite for remembering information (Van Zomeren & Brouwer, 1994) and ALL survivors evidence altered attentional abilities, it does not come as a surprise that a number of studies have found decrements in memory and learning abilities in children who have been treated for ALL (Ciesielski et al., 1999; Précourt et al., 2002). Précourt et al. (2002) notes that children who were treated with either radiation or intrathecal chemotherapy alone exhibited a slower learning curve in comparison to healthy controls on the California Verbal Learning Test (CVLT); however, after multiple exposures and rehearsal of information, the intrathecal chemotherapy group performed at a range comparable to healthy controls.

Consistent with the hierarchical model of neuropsychological functioning, “memory” is actually comprised of a number of different skills and results are more readily understood when each component is analyzed separately. For instance, the ability to recall visual material is governed by the visual association area of the occipital lobe whereas auditory information is processed in the superior temporal region (Lezak

et al., 2004). Simply stating that an individual exhibits compromised or impaired memory abilities has little diagnostic or therapeutic value. According to Lezak et al. (2004), the ability to recall previously learned information actually entails three separate processes: input, storage, and retrieval. Input involves processing and interpreting information from sensory organs prior to storage. During the storage process, processed information is transferred from the primary sensory cortex to adjacent association areas (Lezak et al., 2004). Retrieval entails locating previously acquired information (2004). Thus, each of these processes must be examined separately to determine where deficits originate.

Working memory. Schatz et al. (2000, pp. 190) defines working memory as “the ability to temporarily maintain and manipulate information in a limited capacity system.” Information from the senses must first be processed and categorized before it is encoded into storage. Poor performance on working memory tasks suggest that either information is not being sent from the sensory systems, or, that information is not being properly encoded once it reaches the brain. A review of the literature reveals only one formal study of working memory abilities in ALL survivors (Schatz et al., 2000). Schatz et al. (2000) reports that while some ALL survivors evaluated 30 months after diagnosis evidence impairments in working memory, these deficits are not uniform. Thus, alterations in working memory abilities following treatment for ALL are likely to be subtle if detectable at all (2000). Impairments in working memory are more likely to be pronounced in children who are treated with radiation, however (2000), Schatz et al. (2000) proposes that radiation interferes with both encoding and rehearsal, thereby producing poorer performance on neurocognitive tasks.

Visual memory. Consistent with past research which suggests greater impairments in nonverbal abilities, the preponderance of evidence suggests impaired visual memory abilities among ALL survivors (Ciesielski et al., 1999; Mulhern, 1994; Regan & Reeb, 1998). Ciesielski et al. (1999) notes that autopsies of children treated for ALL reveal extensive damage to the mammillary bodies of the frontal lobes, a structure believed to play a pivotal role in visuospatial memory in both humans and primates. This corroborates the findings of Regan and Reeb (1998) who found that ALL survivors performed significantly below healthy controls on the bead memory subtest of the Stanford-Binet as well as immediate recall of the complex figure test. In a meta-analysis conducted by Mulhern (1994), ALL survivors scored below expected norms on four out of six measures of visual memory.

Verbal memory. Although less often included as a dependent variable in studies evaluating neuropsychological impairment among ALL survivors, there is some evidence that auditory memory is negatively affected by radiation and intrathecal chemotherapy as well. Brown and Madan-Swain (1993) note that overall, survivors of ALL performed below expected norms on measures of auditory memory. However, although both the radiation and intrathecal chemotherapy group scored below their healthy siblings, children who had been treated with radiation did not differ from those who had received intrathecal chemotherapy or other treatments (1993). Other studies (e.g. Ciesielski et al., 1999; Kaemingk et al., 2001; Schatz et al., 2000) indicate that while ALL survivors may initially perform worse on single-trial verbal memory tasks, repeated exposure and rehearsal of auditory stimuli eliminate any discrepancies

between ALL survivors and healthy controls, which would suggest that impairments lie within the domain of learning as opposed to memory.

Executive Functioning.

Executive functioning is comprised of several different skill areas such as planning, processing, sequencing, and shifting from one task to another. However, past research has focused almost exclusively on processing speed as an indice of overall executive functioning. While Brown and Madan-Swain (1993) argue that neuropsychological deficits in executive functioning are variable and specific to the individual, several studies have found a consistent pattern of impairments in processing speed and planning abilities (Ciesielski et al., 1999; Heukrodt et al., 1988; Schatz et al., 2000).

A pivotal factor in predicting performance appears to be the interaction of the specific treatment modality used and age at diagnosis. Regan and Reeb (1998) report greater impairments in processing speed in children who received a combination of radiation and intrathecal chemotherapy in comparison to both healthy controls and children who received the chemotherapy treatment only. However, this finding is based upon differences in performance on the symbol search and coding/ digit span subtests of the WISC-IV. Butler and Copeland (1993) emphasize that the WISC-IV was not intended to detect subtle differences in processing speed or to provide an index of neuropsychological abilities. Thus, readers must be cautious in interpreting the validity of these results.

Among studies which have focused specifically on the effects of intrathecal chemotherapy upon processing speed, Heukrodt et al. (1988) proposes a linear relationship between methotrexate dosage and decrements in processing speed: as the dose of methotrexate increases, the longer the latency in processing speed. Ciesielski et al. (1999) reports similar results, although they note that only ALL survivors who had been diagnosed prior to the age of 5 showed delays in processing speed.

Language

Preliminary studies of language abilities following treatment for ALL suggest mild impairments in both expressive and receptive skills (Anderson et al., 1994; Brown & Madan-Swain, 1993; Espy et al., 2001; Johnston, 1985; Précourt et al., 2002; Taylor, 1987). Deficits have been noted in verbal reasoning (Johnston, 1985; Précourt et al., 2002), word fluency (Espy et al., 2001; Murdoch & Boon, 1999; Taylor, 1987), reading comprehension (Brown & Madan-Swain, 1993), and the ability to follow multi-step oral commands (Johnston, 1985; Murdoch & Boon, 1999). However, some authors (e.g. Brown & Madan-Swain, 1993; Précourt et al., 2002) maintain that these difficulties are a function of impairments in attention and memory and thus, are not truly *language* problems. Précourt et al. (2002) notes that ALL survivors were differentiated from controls by their performance on four of the subtests comprising the freedom from distractibility score; these subtests entail long-term retrieval, abstract reasoning, and lexical attention and thus, are not a pure measure of language skills. Conversely, Taylor et al. (1987) evaluated 52 children using the Token test, a reliable instrument that specifically targets language comprehension and word fluency skills; in comparison to

their healthy siblings, the children treated for ALL performed significantly worse on both measures (Taylor, 1987)

The discrepancies in research findings may be partially explained by the developmental stage of the child at diagnosis (Brown & Madan-Swain, 1993; Reeb & Regan, 1998). The critical period for language acquisition occurs prior to the age of 4 (Brown & Madan-Swain, 1993; Pinker, 1995); thus, children diagnosed and treated during the pre-school years are more likely to demonstrate language deficits than those who are treated at an older age.

In spite of the above findings, several authors (e.g. Johnston, 1985; Murdoch & Boon, 1999) maintain that the true extent of language impairments among ALL survivors remains unknown as a result of over-reliance upon IQ tests to measure language functioning. Historically researchers have depended upon VIQ-PIQ splits and subtest scatter to predict both receptive and expressive language problems. Murdoch & Boon (1999) maintain that even studies which have used appropriate language-based measurements fail to support the broad conclusions about the deleterious effects of central nervous system therapy upon children afflicted with ALL. For instance, a study conducted by Copeland (1996) concluded that language abilities are unaffected by central nervous system therapy; however, these findings were based upon ALL survivors' performance on three brief semantic measures, which Murdoch & Boon (1999) argue are insufficient in gauging subtle changes.

Visuospatial Abilities

There is little disagreement as to alterations in visuospatial abilities following treatment for ALL; virtually all studies suggest impairments in visual-motor integration (Brown & Madan-Swain, 1993; Brown et al., 1998; Ciesielski et al., 1990; Kaemingk et al., 2004; Lesnik et al., 1998; National Cancer Institute, 2005a; Précourt et al., 2002; Regan & Reeb, 1998). Greater decrements have been noted among patients receiving a combined radiation/ intrathecal chemotherapy treatment (Brown et al., 1998; Espy et al., 2001; Lesnik et al., 1998; Regan & Reeb, 1998). According to Espy et al. (2001), children who had been treated with both radiation and chemotherapy evidenced an average decrease of 3.12 points per year on the Beery-Burrkey Visual Motor Integration Test in comparison to an average decrease of .95 points for the chemotherapy-only group; over a four year time span, the discrepancy between the two groups increased, with the combined treatment group scoring 12 points lower than the chemotherapy-only group. Frutiger et al. (1999) note that decrements in visuospatial abilities may persist even after treatment ceases and other visual processes have returned to normal.

However, researchers do not agree on which processes are the most affected. Like memory, visuospatial abilities can be subdivided into *input* processes, *output* processes, and *integration* of visual and motor skills (Brown & Madan-Swain, 1993; Regan & Reeb, 1998). Although several researchers have suggested impairments in visual organization (Regan & Reeb, 1998) and fine motor speed (Espy et al., 2001; Schatz et al., 2000), no study to date has undertaken the task of measuring each individual component of visuospatial skills.

Intellectual Ability

The preponderance of research supports a decline in intellectual functioning following treatment for ALL (Brown & Madan-Swain, 1993; Cousens, 1988; Kaemingk et al., 2004; Mulhern, 1994; Said et al., 1989; Schatz et al., 2000). Most ALL survivors evidence decrements of 2/3 to 1 standard deviation, or approximately 10-11 points, on standard intellectual measures within 7 years following treatment (Brown & Madan-Swain, 1993; Cousens, 1988; Said et al., 1989; Schatz et al., 2000). Although the nature of most intellectual measures render it impossible to pinpoint specific areas of impairment, it has been hypothesized that the decrements in intellectual functioning are attributable to impairments in motor agility, memory, and problem solving (Brown & Madan-Swain, 1993; Schatz et al., 2000; Waber, Isquith, & Kahn, 1994). As with other measures of cognitive abilities, the younger the age of the child at diagnosis, the poorer the performance on measures of global intellectual ability (Said et al., 1989). Preliminary research has not found a relationship between intellectual functioning and treatment modality (Williams et al., 1986). In a study conducted by Williams et al. (1986), children who received 2400 Gy of radiation performed at the same level as their peers who had been treated with much lower doses of radiation. Précourt et al. (2002) notes that children treated with intrathecal methotrexate did not differ from controls on the WISC-III.

Academic Achievement

Given the importance of higher education in attaining career goals, it is not surprising that academic achievement has been used to gauge the ecological validity of studies concerning cognitive difficulties in ALL survivors. Nearly 1/3 of children who

have been treated for ALL evidence academic problems sufficient to meet eligibility for special education (Mauer et al., 1993; Stehbens et al., 1991). This number may underestimate the true extent of learning problems attributable to cancer treatment as Stehbens et al. (1991) notes that over 70% of ALL survivors have sought academic remediation both within and outside of the school environment. Studies indicate that impairments are most frequently found in mathematical abilities and spelling (Brown & Madan-Swain, 1993; Espy et al., 2001; Kaemingk et al., 2004; Kleinman & Waber, 1992; Martin, 2002; Moleski, 2000; Said et al., 1989; Temple, 1997).

Although several authors (e.g. Brown & Madan-Swain, 1993; Said et al., 1989) have noted mathematical impairments as evidenced by poor performance on the arithmetic, digit span, and coding subtests of the WISC-R and WISC-IV, Kaemingk et al. (2004) maintains that both math reasoning and math application skills must be addressed before concluding that a child has a math disability. The majority of studies which have examined academic achievement in ALL survivors typically rely upon information obtained as part of intellectual assessment (Kaemingk et al., 2004). Both the arithmetic and digit span subtests of the WISC-IV are heavily reliant upon working memory whereas coding is more predictive of visuomotor integration, short-term memory, and attention as opposed to mathematical ability (Sattler, 1992).

In regard to reading and spelling abilities, research suggests impairments in phonological skills, but not orthographic abilities (Kleinman & Waber, 1992). According to Kleinman and Waber (1992), the frequency of phonological errors was more pronounced in children who had been treated for ALL prior to the age of 5. Thus, it appears that deficits in reading and spelling, as well as verbal fluency, may be a result

of poor understanding of the relationship between letters and sounds in contrast to a true aphasia (Hebben & Milberg, 2002; Kleinman & Waber, 1992).

Summary and Rationale for Research Study

Based on the information above, it is evident that past efforts to assess neuropsychological functioning in ALL survivors have been confounded by six factors: (1) variations in treatment protocols (Brown & Madan-Swain, 1993; Butler & Copeland, 1993; Moleski, 2000; Schatz et al., 2000; Stehbens et al., 1994); (2) the age and gender of child at diagnosis (Brown & Madan-Swain, 1993; Copeland et al., 1996; Moleski, 2000; Mulhernnn, 1994; NCI, 2005a; Regan & Reeb, 1998; Smith et al., 2005; Stehbens et al., 1994); (3) latency between final treatment session and neurocognitive evaluation (Brouwers et al., 1985; Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Packer et al., 1987; Schatz et al., 2000; Stehbens et al., 1994); (4) use of appropriate comparison groups (Brown & Madan-Swain, 1993; Giralt et al., 1992; Jannoun, 1983; Liu et al., 1996; Moleski, 2000; Moss et al., 1981; Regan & Reeb, 1998; Schatz et al., 2000; Twaddle et al., 1983); (5) measurement of neuropsychological functioning in pediatric populations (Butler & Copeland, 1993; Eiser, 1992; Précourt et al., 2002; Regan & Reeb, 1998); and (6) a tendency to treat the various subcomponents of neuropsychological functioning as isolated processes that operate independent of one another (Ciesielski et al., 1999; Lockwood et al., 1999; Hebben & Milberg, 2002). While both past and current research in this area provides a strong foundation upon which future studies can elaborate on specific areas of impairment among ALL survivors, results have been equivocal and insufficient to identify effective interventions. Furthermore, despite conclusive results from neuroimaging studies which support a

hierarchical model of neuropsychological functioning (Ciesielski et al., 1999; Hebben & Milberg, 2002), no study to date has addressed the relative influence of more basic cognitive abilities in predicting performance on higher-order tasks such as executive functioning or language. Thus, it is the intent of this study to address neuropsychological impairments in ALL survivors using a hierarchical model in which deficits in “basic” cognitive skills, such as sensory awareness and attention, are taken into account prior to examining more complex functions such as executive functioning. Specifically, the following hypotheses will be addressed: (1) differences in sensorimotor skills, attention, memory, and visuospatial skills as a function of specific treatment type; (2) influence of latency between final treatment session and neuropsychological testing; (3) covariate effect of age as a predictor of performance on neuropsychological measures; (4) differences on neuropsychological measures as a function of gender; (5) performance on the NEPSY in comparison to past research studies which have documented impairments in sensorimotor abilities, attention, memory, and visuospatial skills; and (6) hierarchical structure of neuropsychological functioning in survivors of ALL.

Hypothesis 1: Performance on Neuropsychological Measures Will Fall on a Continuum with the Combined Treatment Group Showing the Greatest Impairments, Followed by the Radiation-Only Group, and Then the Chemotherapy-Only Group.

Past research has demonstrated that both cranial irradiation and intrathecal administration of specific chemotherapeutic agents such as methotrexate can have deleterious effects upon the developing brain (Butler & Copeland, 1993; MacLean et al., 1995; Moleski, 2000; Stehbens et al., 1994). While no study to date has made direct

comparisons of neuropsychological functioning among children treated with radiation, chemotherapy, or a combination thereof, research has shown that methotrexate and other commonly used chemotherapeutic agents augment the effects of radiation treatment (Copeland, 1996; Dufner et al., 1984; Mauer, 1983; NCI, 2005a). However, past research efforts have focused on comparisons between children diagnosed with ALL and 1 of 2 control groups: (1) age-matched peers who have undergone similar treatment protocols for brain tumors, or (2) healthy siblings of ALL patients. While the former provides valuable information regarding the specific impact of the ALL disease process upon cognitive functioning and the latter controls for genetic influences, neither addresses the question of how different *treatment modalities* affect neuropsychological functioning among ALL survivors. Subsequently, it is hypothesized that children who received combination treatment will demonstrate poorer performance on measures of sensorimotor skills, attention, memory, and visuospatial skills. Furthermore, given the wealth of research which has documented both the short-term and long-term alterations in neurocognitive functioning as a result of radiation treatment, it is expected that children who received radiation-only treatment will evidence greater impairments on the aforementioned neuropsychological domains in comparison to children who were treated solely with chemotherapy. Thus, in comparing all three treatment modalities, it is anticipated that performance on neurocognitive measures will fall on a continuum with the combined treatment group showing the greatest impairments, followed by the radiation-only group.

Hypothesis 2: Impairments in Neuropsychological Functioning Will be Apparent a Minimum of 2 Years Post-Treatment.

It is important to note as well that *when* a child is evaluated in relation to initial diagnosis can substantially affect performance on neuropsychological measures. Due to the gradual, continuous maturation of the brain during childhood & structural alterations that result in neuropsychological impairments that are not evident until later stages of development, ALL survivors may not evidence signs of neurocognitive impairments until several years later. While an exact latency period between initial diagnosis and evidence of neuropsychological alterations has not been established, past studies suggest that children should not be evaluated any earlier than one year after their final treatment. Consistent with this finding, it is hypothesized that children who were assessed a minimum of two years after treatment will show neurocognitive impairments.

Hypotheses 3: Performance On Neuropsychological Measures Will Vary with Age, with Children Who Were Diagnosed Prior to the Age of 5 Showing Greater Impairments in Comparison to Children Diagnosed with ALL After Age 5.

Research has also demonstrated a link between both age at diagnosis and gender in predicting long-term cognitive functioning (Brown & Madan-Swain, 1993; Butler & Copeland, 1993; Moleski, 2000; Regan & Reeb, 1998; Stehbins et al., 1994). Because the brain and central nervous system continue to mature throughout childhood and young adulthood, children who are diagnosed with ALL at a young age are at an increased risk for difficulties with attention, concentration, memory, fine motor skills, and visuospatial abilities (Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Guyton & Hall, 1996; Moleski, 2000). It is suspected that treatment for ALL prior to the age of 5

can result in a disruption in myelinazation and cortical atrophy (Fletcher & Copeland, 1988; Moleski, 2000; Reeb & Regan, 1998). However, it is important to note that many of these conclusions are based upon performance on standardized IQ tests, which may be insensitive to subtle changes in neuropsychological performance. In addition, until recently there have not any neuropsychological instruments which have been empirically validated with pre-school age children. Thus, it could be that the arbitrary age distinction of under 5 versus over 5 is an artifact of the instruments being used as opposed to an actual age difference. Subsequently, age at diagnosis will be used as a covariate in this study to determine if it accounts for a significant amount of variance when using a developmentally-appropriate battery specifically designed for young children.

Hypotheses 4: Females Will Evidence Lower Scores on All Measures of Neurocognitive Abilities in Comparison to Their Male Counterparts.

Past research has conclusively shown that gender reliably predicts performance on neuropsychological measures among ALL survivors. Specifically, greater impairments have been noted among females. It is unclear at the present time where specific gender differences in neuropsychological functioning exist. For this reason, it is hypothesized that females will evidence lower scores on all measures of neurocognitive abilities in comparison to their male counterparts.

Hypotheses 5: Performance on the NEPSY Will Be Consistent with Past Research Studies Documenting the Impact of ALL upon Neuropsychological Functioning; Survivors Are Likely to Demonstrate Impairments in Sensorimotor Abilities, Attention, Memory, and Visuospatial Skills.

The choice of which dependent measure(s) to use in evaluating the presence and magnitude of differences among various treatment groups can influence the outcome of a research study: past research has often relied upon intellectual measures which have been criticized for being insensitive to subtle changes in cognitive functioning, a poor indicator of neuropsychological functioning, and for using tasks that simultaneously measure more than one skill, thereby rendering the process of delineating underlying neurocognitive deficits extremely difficult. Furthermore, despite the plethora of research findings that suggest greater impairments among children treated at a younger age, there are few neuropsychological measures that have been empirically validated for use with pre-school age and younger children. To date, the NEPSY is the only comprehensive measure of neurocognitive performance that is intended for children under the age of 5. Thus, while this study is not the first to address neuropsychological functioning in pediatric ALL survivors, it is novel in its approach through the use of the NEPSY, a comprehensive neuropsychological battery specifically designed for use with children ages 3-12. It is anticipated that the results of this study will support past research findings, although the magnitude and origin of neurocognitive impairments may vary in comparison.

Hypothesis 6: Performance On Neuropsychological Measures Will be Consistent with a Hierarchical Model in which Sensorimotor Abilities Account For the Most Variance, Followed by Attention, Memory, and Finally Visuomotor Skills.

Consistent with the hierarchical model of neuropsychological functioning proposed by Aleksandr Luria, this research study seeks to delineate the individual contributions of more basic cognitive skills in predicting performance on neuropsychological measures using a step-wise procedure. That is, as opposed to treating all of the dependent variables as solitary measures that operate independent of each other and are of all equal magnitude, alterations in more basic cognitive skills (e.g. attention, fine motor skills) are given higher priority over higher-order processes (e.g. abstract reasoning, organization) in predicting neuropsychological functioning. Thus, it is hypothesized that performance on neuropsychological measures will be consistent with a hierarchical model in which sensorimotor abilities account for the most variance, followed by attention, memory, and finally visuomotor skills. Because this is the first study to employ a hierarchical model of neuropsychological functioning in ALL survivors, predictions regarding group differences will be explored via post-hoc analysis contingent upon significant main effects.

Other Considerations

While it would be intriguing to examine all domains of neuropsychological functioning among ALL survivors, past research has only consistently shown alterations in sensorimotor abilities, attention, memory, and visuospatial skills; efforts to elucidate the long-term effects upon language and executive functioning skills has resulted in equivocal finding (Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Reeb &

Regan, 1998; Stehbins et al., 1994). This is consistent with the finding that ALL survivors evidence greater impairments in skills associated with the right hemisphere (Brown & Madan-Swain, 1993; Reeb & Regan, 1998; Stehbins et al., 1994). Further evidence to support a relationship between treatment for ALL and disruptions in nonverbal skills is provided by Packer et al. (1987), who note that methotrexate interferes with the production of a key lipid necessary for myelin formation. Because the right hemisphere has been shown to be the area of the most intense myelinization during childhood (Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Moleski, 2000; Reeb & Regan, 1998), it is logical to conclude that skills associated with this area will show the greatest decline. Thus, for the purposes of this study, only functioning in the following areas will be assessed: sensorimotor skills, attention, memory, and visuospatial abilities.

Finally, because executive functioning is mediated by the frontal lobes and not considered a lateralized ability, measures of processing speed, planning, and abstract reasoning will also be excluded from this study (Lezak, Howieson, & Loring, 2004). In addition, neither academic achievement nor general cognitive ability will be included as dependent measures based upon previous research which suggests that both are poor indicators of neuropsychological functioning (Butler & Copeland, 1993; Eiser, 1992; Moleski, 2000; Reeb & Regan, 1998).

CHAPTER 2: METHODS

Participants

All information was taken from a database maintained by the behavioral health department of a large, metropolitan, children's specialty hospital. Only information for children ages 1-12 who had been treated for acute lymphocytic leukemia from 2002-2005 and who were administered the core domains of the NEPSY were included in this study. 90 children (28 females, 52 males) ages 3 to 12 ($M = 7.28$ years, $SD = 2.64$) were evaluated. Patients ranged in age from 1 to 12 ($M = 4.97$ years, $SD = 2.76$) at initial diagnosis. Only test scores that were obtained a minimum of 2 years after the child's final cancer treatment were included.

Materials

NEPSY Neuropsychological Battery for Children. The NEPSY is a comprehensive neuropsychological instrument intended for use with children ages 3-12. Based upon the Lurian model, the NEPSY yields five domain scores: *sensorimotor abilities* (fingertip tapping, imitating hand positions, visuomotor precision, manual motor sequences, finger discrimination), *attention-executive* (tower, auditory attention and response set, visual attention, statue), *memory and learning* (memory for faces, memory for names, narrative memory, sentence repetition, list learning), *visuospatial skills* (design copying, arrows, block construction, route finding), and *language* (body parts naming, phonological processing, speeded naming, comprehension of instructions, repetition of nonsense words, verbal fluency, oromotor sequencing) (Korkman, Kirk, & Kemp, 1998). Only the attention/executive, memory/learning, visuospatial, and sensorimotor domain scores were examined in this study. Functioning in each domain is comprised of

graduated subtests; there are 27 subtests in all (five sensorimotor, six attention-executive, five memory/ learning, four visuospatial, and seven language) (Korkman et al., 1998). Raw scores were converted into age-based scaled scores. Individual subtest scores were not recorded during data collection and thus, were not available for more in-depth analysis.

The NEPSY was standardized using a random sample of children and reflects adequate representation of minorities based upon 1995 Census Data (Korkman et al., 1998). There are two forms; one is for children ages 3-4 and the other is for ages 5-12. The core domain scores have moderate-high internal consistency scores and are listed from lowest to highest as follows: sensorimotor (.79), attention/ executive (.82), visuospatial processing (.83), language (.87) and memory and learning (.87) (Ahmed & Warriner, 2001; Korkman et al., 1998). Stability coefficients for the domain scores are as follows: attention/ executive (.68), language (.78), sensorimotor (.77), visuospatial (.72), and memory and learning (.90) (Korkman et al., 1998).

The NEPSY is intended as a flexible battery in which areas of weakness or strength can be further explored based upon performance on core domains. All individuals in this study were administered the core domain subtests; any additional neuropsychological testing was not included in this study. The subtests comprising the core battery are as follows: *Sensorimotor* - fingertip tapping, imitating hand positions, visuomotor precision; *Attention/ Executive Functioning* - tower, auditory attention and response set, visual attention; *Memory/ Learning* - memory for faces, memory for names, narrative memory; *Visuospatial*- design copying, arrows.

Design and Procedure

Although a 3 x 2 factorial MANCOVA was initially proposed, a review of the de-identified database revealed that none of the subjects had received radiation alone; thus, the Treatment variable only had 2 levels, rendering a 2 x 2 design. Type of treatment (chemotherapy only vs. combined treatment) and Gender (male vs. female) were independent variables and the sensorimotor, attention/ executive, memory and learning, and visuospatial standard scores of the NEPSY were used as dependent variables. Each of these domains was analyzed sequentially via a Roy-Bargmann step down test so that performance differences due to more basic functions were eliminated prior to addressing higher-order neurocognitive functioning. Age at diagnosis (under age 5 vs. over age 5) was used as a covariate.

To ensure confidentiality, all identifying information contained within the behavioral health department's database was eliminated prior to being released to the principal investigator. Because all identifying information was removed prior to analyses, neither individual informed consent nor information concerning the availability of the results of this study were made available.

CHAPTER 3: RESULTS

A 2 x 2 between-subjects multivariate analysis of covariance was performed on four dependent variables: sensorimotor, attention/executive skills, memory/learning, and visuospatial abilities; the standard score for each of the above domains was used, as opposed to the individual subtests of the NEPSY. Independent variables were gender and treatment modality; the covariate was a categorical age variable based on whether the child had been diagnosed with ALL prior to the age of 5.

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MANCOVA was used for the analysis with the sequential adjustment for nonorthogonality. Order of entry was sensorimotor, attention/executive, memory/learning, and then visuospatial standard scores followed by the covariate. Total N of 91 was reduced to 81 due to missing NEPSY scores. There were no univariate or multivariate within-cell outliers at $p < .001$. Results of evaluation of assumptions of homogeneity of variance-covariance matrices, linearity, and multicollinearity were all within an acceptable range. However, there was an unequal distribution of patients in the chemotherapy-only versus combined treatment group when partitioned by gender: males (N = 33) and females (N=29) in the chemotherapy-only group significantly outnumbered males (N = 18) and females (N = 9) in the combined treatment group.

Examination of each group and their variances revealed that the largest amount of variance occurred within the chemotherapy-only female group and chemotherapy-only male group, respectively. The female combined group, which had the smallest cell size, showed the least amount of variance. F_{Max} was judged to be within an average range, so in accordance with Tabachnick and Fidell (2001), the analysis proceeded.

The overall multivariate model, using Pillai's criterion, was not significant, $\Lambda(4, 81) = .31302$, $p = .869$. There were no interaction or main effects for treatment type or gender. Power for the overall multivariate model was determined to be poor (.117).

Age at diagnosis (prior to age 5 vs. after age 5), served as a covariate. Age at diagnosis provided significant adjustment to sensorimotor skills, with $\beta = .334$, $t(77) = 4.80$, $p = .002$. Children diagnosed prior to the age of 5 had significantly lower scores on the NEPSY sensorimotor domain ($M = 20.61$, $SD = 6.43$) in comparison to children diagnosed at age 6 or older ($M = 25.42$, $SD = 6.23$). The covariate also provided significant adjustment to attention/executive functioning, with $\beta = .2266$, $t(77) = 3.163$, $p = .034$. Children in the under age 5 category scored significantly lower on the attention/executive functioning domain ($M = 24.35$, $SD = 6.37$) in comparison to those in the age 6-12 category ($M = 27.38$, $SD = 6.23$). Finally, age at diagnosis was significant for memory, with $\beta = .338$, $t(77) = 5.66$, $p = .002$. Again, children in the younger age group scored significantly lower on the NEPSY memory domain ($M = 24.93$, $SD = 7.80$) when compared to over age 5 category ($M = 30.49$, $SD = 6.19$).

To determine the influence of each main effect on the individual dependent measures, a Roy-Bargmann stepdown analysis was performed on the prioritized dependent variables (DVs). All variables were judged to be sufficiently reliable to warrant stepdown analysis. In stepdown analysis each DV was analyzed, in turn, with higher-priority DVs treated as covariates and with the highest-priority DV tested in a univariate ANOVA. Homogeneity of regression was achieved for all components of the stepdown analysis. An experiment-wise error rate of 5% was achieved by the apportionment of alpha.

Exploratory analysis revealed a significant effect for NEPSY version, $F(4,83) = 2.97$, $p = .024$. Children who were tested using the 3-4 year-old version ($N = 47$) of the NEPSY scored significantly lower on the sensorimotor, attention/executive, and memory domains in comparison to those tested using the 5-12 year-old ($N = 43$) version. This finding was independent of gender and years since diagnosis.

Pooled within-cell correlations among DVs are shown in Table 3.

CHAPTER 4: DISCUSSION

It was hypothesized that the six following factors would account for differences on neuropsychological measures among children treated for ALL: (1) treatment modality; (2) latency between final treatment and neuropsychological testing; (3) age at diagnosis; (4) gender; (5) choice of neurocognitive assessment material; and (6) a hierarchical structure in which more basic cognitive functions account for the greatest variance in scores followed by more abstract concepts. A hierarchical model in which “lower order” (i.e. more basic) cognitive abilities were analyzed prior to more advanced skills in a step-wise fashion was accomplished via a Roy-Bargmann step-down test. The order in which variables were entered is as follows: sensorimotor skills, attention/executive functioning, memory/learning, and visuospatial abilities. Results are discussed as they relate to the initial 6 hypotheses.

Hypothesis 1: Performance on Neuropsychological Measures Will Fall on a Continuum with the Combined Treatment Group Showing the Greatest Impairments, Followed by the Radiation-Only Group, and Then the Chemotherapy-Only Group.

Because there were no children in the radiation-only group, comparisons were limited to the combined treatment and chemotherapy-only groups. Statistical analysis did not reveal any significant interactions or main effects for treatment type.

No efforts were made to control for specific effects of different chemotherapeutic agents. Past research suggests that specific medications can affect some neurocognitive abilities more than others (Ghalie et al., 1990; Johnston, 1985; Mauer et al., 1983; Memon et al., 1995; Menegaux et al., 1994; Moleski, 2000; Nussbaum et al., 1995). For instance, cisplatin has been linked with speech difficulties and memory

deficits (NCI, 2005) whereas methotrexate is associated with impairments in attention, processing speed, and hand-eye coordination (NCI, 2005). The deleterious effects of these agents may be augmented by radiation therapy; thus, treatment effects in this study may have been masked by failing to distinguish between specific drug protocols.

Although treatment differences between children treated with chemotherapy alone versus combined chemotherapy/radiation were documented in this study, efforts were not made to control for relapses or subsequent rounds of therapy. Children who underwent a bone marrow transplant were not distinguished from those who were successfully treated with a single round of chemotherapy. Williams et al. (1986) argues that more aggressive treatment methods are likely to result in more severe deficits. Patchell et al. (1985) notes that in addition to the deleterious effects of chemotherapy and radiation, bone marrow transplant recipients are vulnerable to the risks of neurotoxicity arising from preparatory regimens, infections secondary to immunosuppression, and complications of the central nervous system as a result of multi-organ system failure. Transplant recipients may develop acute graft versus host disease, which is typically treated with corticosteroids; prolonged use of certain corticosteroids has been linked with reduced hippocampal size (Brown et al., 2004) and mental depression (Cool, 1991). However, previous attempts to isolate neurocognitive impairments following bone marrow transplant have been difficult as a result of heterogeneous populations and high mortality rates (Cool, 1991).

Hypothesis 2: Impairments in Neuropsychological Functioning Will be Apparent a Minimum of 2 Years Post-Treatment.

While the precise period at which children treated for ALL begin to evidence neurocognitive impairments was not evaluated in this study, results do not support a 2 year latency period. The precise latency between when a treatment course ends and when the child is evaluated using neurocognitive measures is an important factor that was not taken into consideration in this study. Given the non-linear development of neuropsychological abilities, it is difficult to determine at what point all neurological “late effects” will be evident (Brouwers et al., 1985; Brown & Madan-Swain, 1993; Fletcher & Copeland, 1988; Packer et al., 1987; Schatz et al., 2000; Stehbens et al., 1994). For instance, impairments in fine motor skills have been documented as early as 1 year post-treatment (Moleski, 2000) whereas difficulties in verbal processing and verbal memory may not be apparent until 3-5 years later (Mulhern et al., 1988; Précourt et al.,). As Packer et al., (1987) points out, few studies have made efforts to ensure that an adequate period of time has elapsed in order for late effects to emerge, choosing instead to just “randomly” guess. It is suggested that future studies allow a minimum of 5 years between the final treatment session and neuropsychological evaluation.

In addition, as De Luca et al. (2003) and Welsh et al. (1991) note, neuropsychological development varies for discrete functions and thus, the *age* of the child as well as the *latency* between treatment and neuropsychological testing must be taken into consideration. For instance, improvements in vigilance are most notable between ages 4-6 whereas selective attention shows a bimodal pattern in which skills improve significantly from 4-6 and then later between ages 8-10 (Espy & Bull, 2005;

Klimkeit et al., 2004); thus, a child who is diagnosed at age 9 may not evidence problems in these areas. Support for this age/test latency interaction is evidenced by a study conducted by Stehbens et al. (1994), in which children were tested using the WISC-R, Token Test for Children, Rapid Automatized Naming Test, RAVLT, FAS Fluency, and Sentence Repetition Test. Results indicate that neurocognitive difficulties were evident 9 months post-treatment in children who were diagnosed before the age of 5, but were not evident in those children who were older at diagnosis (Stehbens et al., 1994). Thus, it could be that the older the child is at diagnosis, the longer it will take for late effects to emerge.

Furthermore, measures of inhibition may be confounded by the delayed development of motor skills: according to a study conducted by Dowsett & Livesey (2000), young children were able to respond appropriately on measures of verbal inhibition but when given a task that required motor inhibition, they scored poorly. Efforts should be made to differentiate test items so that the influence of motor movements can be analyzed independent of processing speed and other neurocognitive abilities.

Hypotheses 3: Performance On Neuropsychological Measures Will Vary with Age, with Children Who Were Diagnosed Prior to the Age of 5 Showing Greater Impairments in Comparison to Children Diagnosed with ALL After Age 5.

Age was used as a covariate in this study and was statistically significant; children who were diagnosed prior to the age of 5 scored significantly lower on 3 of the 4 dependent measures of the NEPSY: sensorimotor abilities, attention/executive functioning, and memory. It should be noted that while the cut-off age of 5 was based

upon past research studies, this is an arbitrary number. Efforts have focused on differences between pre-school age children and school-age children; a definitive age at which treatment for ALL poses less of a risk of neurocognitive impairments has not been established, although it is generally accepted that the younger a child is when treatment begins, the more likely one will experience difficulties with attention, memory, and sensorimotor skills.

Although efforts were made to ensure use of measures that are appropriate for pediatric populations, this study did not take into account the developmental trajectory of neuropsychological functioning. Research indicates that neuropsychological skills do not develop in a linear fashion, but rather progress in spurts or stages (De Luca et al., 2003; Espy & Bull, 2005). Executive functioning skills may be evident as early as 12 months but do not stabilize until late adolescence or early adulthood (De Luca et al., 2003).

It also appears evident that the manner in which such skills are measured and how they are defined may differ by age. For instance, Zelazo et al. (2003) notes that cognitive inflexibility may be labeled as perseveration depending on what age population is being targeted. Furthermore, a single term may be used to indicate two different types of skills, as evidenced by the fact that “inhibition” can refer to both cognitive inflexibility and the failure to suppress an incorrect response despite awareness of the correct answer (Zelazo et al., 2003).

Consistent with the findings that the validity and sensitivity of measures vary by age, similar tasks purported to gauge a specific construct may actually be assessing different skills depending on the age of the child (Beveridge et al., 2002; Hughes et al.,

2002). As Hughes (2002) points out, the cognitive demands of a specific task such as the Tower of London may not be the same at age 8 as they are at age 6. Furthermore, differences on such tasks may reflect different factors in children than in adults; for instance, a depressed processing speed score may be the result of synaptic pruning in children in comparison to localized brain damage in an adult (Hale et al., 1997; Klenberg et al., 2001).

In addition, the significant differences between the children diagnosed prior to age 5 and those diagnosed after age 6 may be an artifact of different versions of the same test for different age categories. Exploratory analysis revealed that children tested using the 3-4 year old version of the NEPSY scored significantly lower on the sensorimotor, attention/executive functioning, and memory domains in comparison to children tested using the 5-12 year old protocol. Although the two versions are very similar and contain many of the same subtests, the battery for older children is more extensive. It is possible that the battery for the 3-4 year old group is measuring different constructs than that of the 5-12 year old group and thus, any identified differences between the two groups would be a function of different constructs being measured as opposed to an actual effect for age.

Hypotheses 4: Females Will Evidence Lower Scores on All Measures of Neurocognitive Abilities in Comparison to Their Male Counterparts.

Males and females evidenced similar performance on all measures of neurocognitive functioning. However, males comprised 66% of the population; in combination with the low *N*, it is possible that power was insufficient in detecting gender differences. The absence of any significant gender differences may also be related to

the interaction of age and the use of generalized measures of attention/executive functioning. Males and females show distinct patterns of strengths and weaknesses among *specific* measures of attention, such as selective attention versus alternating attention (Klenberg et al., 2001). These patterns change as the child develops and then plateau in early adulthood (De Luca et al., 2003). For instance, in a study conducted by Klenberg et al. (2001), girls under the age of 6 had significantly higher scores on measures of inhibition, selective attention, and verbal fluency in comparison to their male counterparts; however, boys performed equally as well as girls on the same measures after age 6 (Klenberg et al., 2001).

Hypotheses 5: Performance on the NEPSY Will Be Consistent with Past Research Studies Documenting the Impact of ALL upon Neuropsychological Functioning; Survivors Are Likely to Demonstrate Impairments in Sensorimotor Abilities, Attention, Memory, and Visuospatial Skills.

Unlike past research studies, the results of this study did not support neurocognitive impairments in the areas of sensorimotor abilities, attention, memory, or visuospatial skills among ALL survivors beyond what was accounted for by age of diagnosis. While children diagnosed prior to age 5 showed impairments in sensorimotor abilities, attention, and memory, there were not any significant differences in neurocognitive skills among children age 6 or older. However, because this study focused on differences in neuropsychological functioning as a function of treatment modality, patients were not compared to a control group consisting of normal children. It is likely that children who were diagnosed after age 6 showed differences on

neurocognitive measures in comparison to children who have never been diagnosed with ALL.

This lack of findings in contrast to the many well planned, ecologically sound, research studies of the past may be attributable to differences in the sensitivity of the dependent measure(s). Like many psychological assessment instruments, the NEPSY is comprised of several subtests that are intended to measure discrete functions such as processing speed and visual attention. Specific subtests are combined to yield an overall *domain* score, which is a more generalized measure of neurocognitive abilities. Past research has relied upon various measures which are comparable to the subtest scores of the NEPSY. Because the subtest scores of the NEPSY were not recorded for participants in this study, the generalized domain scores were used for comparison; thus, past studies reporting significant effects relied upon instruments with much greater sensitivity than those used in this study and thereby may have been better able to detect subtle differences. Future research should focus on comparison of individual subtest scores in contrast to global or domain scores.

It should also be noted that while neurocognitive performance can be assessed via both quantitative and qualitative data, there is a tendency to rely more heavily upon quantitative measures as it is regarded as more objective (Anderson, 2002; Beveridge et al., 2002; Hughes, 2000). This limits the measure's diagnostic utility as quantitative data does not reflect important behavioral patterns such as perseveration or specific error patterns (Anderson, 2002). In addition, quantitative data is limited by the "ceiling" effect, thereby masking changes in individuals who perform in the above average or superior range (Beveridge et al., 2002). Hughes (2000) emphasizes the need for both

quantitative and qualitative variables in studying neuropsychological performance. Although the NEPSY includes scoring information for qualitative data (e.g. number of omission versus commission errors), only the standardized scores for the domain scores were included in this study.

An additional consideration is that the skills comprising neuropsychological domain scores may not be the same for pediatric populations as it is for adults, particularly in regard to executive functions. Indeed, how “executive functioning” is operationalized varies according to the population being studied (Carlson, 2005). Hala et al. (2003) posits that executive functioning, as seen in studies involving adult populations, is comprised of working memory, inhibitory control, and attention whereas Anderson (2002) defines *pediatric* executive function as consisting of attention, information processing, cognitive flexibility, and goal setting. Miyake et al. (p. 53, 2000, as cited in Beveridge et al., 2002) points out “the precise nature of executive processes implicated in the performance of these tasks is underspecified...there is a paucity of rigorous theoretical analysis and independent empirical evidence regarding what these executive tasks really measure.”

Despite all of the studies documenting impairments in neuropsychological functioning following treatment for ALL, very few studies have actually performed statistical analyses pre to post-test to determine if these changes in scores are clinically significant. Moss et al. (1981) failed to find a statistically significant difference between a group of children tested 23 months post-treatment in comparison to children tested 47 months post-treatment, despite decrements in performance on neuropsychological measures pre to post-treatment for both groups. Cancer-causing factors or agents may

result in cognitive impairments that are independent of the effects of treatment, age, or gender.

Hypothesis 6: Performance On Neuropsychological Measures Will be Consistent with a Hierarchical Model in which Sensorimotor Abilities Account For the Most Variance, Followed by Attention, Memory, and Finally Visuomotor Skills.

This study did not support a hierarchical framework of neuropsychological functioning. Statistical analysis did not reveal that lower order cognitive abilities account for more variance than higher order skills such as planning or problem-solving. It is suspected that this may have been attributable to the reduced power of the analysis as a result of the small population. While statistical power was gauged as “moderate,” the use of the NEPSY domain scores in lieu of individual subtest scores warrants the need for greater power, especially when cell sizes contain less than 20 observations. Future studies should be careful to balance the sensitivity of an instrument with the overall ability to detect a significant finding.

Hierarchical neuropsychological functioning assumes that there are notable differentiations in skills which can be measured as distinct constructs. In adult populations, attention is viewed as operating in tandem with executive abilities although specific skills such as planning and cognitive flexibility can be easily isolated. It stands to reason, then, that children also show a differentiation of skills which would reveal specific deficits during a comprehensive assessment. However, several authors (e.g. Carlson, 2005; Espy & Bull, 2005) have posited that because of the uneven development of specific neurocognitive abilities, neuropsychological functioning may not be hierarchically structured in childhood, but rather consist of generalized abilities that

develop into highly specialized skills during the latter part of adolescence and early adulthood. Consistent with this hypothesis, Schmitt et al. (2004) found that the attention/executive functioning domain of the NEPSY did not differentiate between brain-injured and non brain-injured subjects. In fact, only the language and sensorimotor domains of the NEPSY were effective in discriminating between the two groups; the memory and learning domain was unaffected by changes in visual memory and the visuospatial domain provided no discriminate validity at all (Schmitt et al., 2004). De Luca et al. (2003) found similar results when assessing set-shifting abilities among 8 and 10 year-old children. In addition, Espy and Bull (2005) found no differences in 4-5 year-olds when evaluating the influence of proactive interference versus resistance to distraction.

However, as Carlson (2005) points out, neuropsychological measures are often factorially complex; many tasks purported to be “pure” measures of a specific skill may actually tap into several different abilities. Since the core domain of the NEPSY is intended as a neuropsychological screener, it is possible that the relative weakness of the attention/executive, visuospatial, and memory/learning domain scores in differentiating brain-injured from non brain-injured subjects may be attributable to the instrument’s insensitivity to subtle differences rather than a lack of skill differentiation.

Finally, the unique contribution of genetics, brain development, and different treatment modalities may have resulted in such distinct pattern of strengths and weaknesses that broad generalizations about the population cannot be accurately inferred. Rourke (1989) notes that one of the most common errors in studies focusing on pediatric populations is assuming that every child with a given illness will show the

same response pattern throughout development. However, two children with the same medical diagnosis may show very different neuropsychological profiles depending on treatment variables, developmental stage of brain at initial diagnosis, frequency and use of interventions to remediate deficits, and other factors. Detailed information about these factors should be included in future research studies to reduce confounding effects.

Taken all together, the results of this study do not support a hierarchical structure of neuropsychological abilities in children treated for ALL. However, general conclusions are tenuous due to the unequal distribution of subjects in the male and female chemotherapy groups in comparison to the male and female combined treatment groups. Age at diagnosis (before age 5 versus after age 6) appears to be a strong predictor of long-term cognitive functioning. Based on the results of past studies, it appears evident that there is a latency between when treatment ends and when neurocognitive impairments become evident; however, the exact time frame in which deficits emerge remains unknown. Finally, the failure to control for specific chemotherapeutic agents may have resulted in masking group differences.

CHAPTER 5: IMPLICATIONS

The results of this study have important implications for clinicians who work with children being treated for ALL. The relationship among age at diagnosis, treatment modality, latency of testing, and neurocognitive abilities appears to be more complicated than originally believed; thus, one cannot accurately deduce that all children treated for ALL will manifest the same pattern of impairments. Clinicians should be cognizant of the fact that neuropsychological functioning does not proceed in a linear fashion and therefore, assessment should focus on the skills that are developmentally appropriate for the child (Carlson, 2005; De Luca et al., 2003; Espy & Bull, 2005). For instance, measures of inhibition in young children should be limited to verbal tasks as studies have shown that motor skills are not fully developed until a later period in time (Dowsett & Livesey, 2000). Abstract reasoning does not stabilize until adolescence and therefore, results pertaining to this skill in young children are likely to be confounded by developmental limitations (Espy & Bull, 2005; Klimkeit et al., 2004).

Furthermore, it appears evident that assessment of neurocognitive functioning should focus on specific constructs as opposed to general domains (Beveridge et al., 2002; Hughes et al., 2002). Improvements in selective attention are likely to be masked by a domain score that reflects performance on vigilance, inhibition, and sustained attention (Klenberg et al., 2001). Alterations in visual memory, which would be consistent with the theory of greater right hemisphere dysfunction, “disappear” when combined with verbal memory to get an overall memory score (Klenberg et al., 2001; Schmitt et al., 2004). Clinicians should be encouraged to only evaluate specific

constructs depending on the child's developmental level as opposed to doing broad screenings.

The results of this study further implicate a need for frequent, thorough evaluation of the child's academic progress and increased communication between medical professionals and school staff. ALL survivors are at an increased risk for problems with various neuropsychological skills dependent upon the interaction of several factors. Teachers should be apprised of a child's academic weaknesses and given suggestions for effective classroom accommodations.

Furthermore, for children who have been treated for ALL who are at an increased risk for learning problems due to genetics or specific chemotherapeutic agents, preventative techniques aimed at reducing the severity of neurocognitive impairments should be implemented. Several promising studies (e.g. Butler & Mulhern, 2005) suggest that the use of certain cognitive-behavioral strategies, mental activities, and medication may be effective in moderating impairments in attention and memory.

Finally, this study suggests that not all treatments for ALL result in neurocognitive impairment. Many children who are successfully treated with milder chemotherapeutic agents intravenously do not evidence the expected deficits in cognitive functioning. Clinicians should be familiar with the most commonly used chemotherapeutic agents and the accompanying side effects which could result in decreased attention, memory, or visuospatial abilities.

Table 1
Subject Characteristics

	<u>Males</u>	<u>Females</u>	<u>Total</u>
Number	51	38	89
Mean age at diagnosis*	5.25	4.63	4.97
Mean age at testing*	7.59	6.92	7.28
Time since diagnosis*	2.83	2.76	2.80
Treatment			
Chemotherapy only	33	29	62
Chemotherapy + radiation	18	9	27

*Time in years

Table 2
Multivariate Statistics

Gender*Treatment

Overall power = .117 (poor)

<u>Variable</u>	<u>Value</u>	<u>Exact F</u>	<u>Hypothesis DF</u>	<u>Error DF</u>	<u>Significance</u>
Pillais	.015	.313	4	81	.869

Roy-Bargman Stepdown F-tests

<u>Variable</u>	<u>Stepdown F</u>	<u>DF</u>	<u>Hypothesis DF</u>	<u>Significance</u>
<i>Sensorimotor Skills</i>	.259	1	84	.612
<i>Attention/Executive</i>	.002	1	83	.963
<i>Memory/Learning</i>	.982	1	82	.325
<i>Visuospatial Abilities</i>	.002	1	81	.872

Table 3

: Mean NEPSY Standard Scores as a Function of Gender and Treatment Modality

	<u>NEPSY Standard Scores</u>			
	Sensorimotor	Attention/Executive	Memory/Learning	Visuospatial
Chemotherapy only	22.13	24.64	27.01	16.85
Female (N=29)	22.67	23.94	26.00	17.45
Male (N=33)	21.66	25.50	27.89	16.32
Chemotherapy + radiation	22.21	26.91	26.32	16.28
Female (N=9)	20.96	24.81	25.77	16.32
Male (N=18)	22.84	27.96	26.60	

Table 4

Significance of Covariate (Age of Diagnosis) on NEPSY Domain Scores

<u>Dependent Variable</u>	<u>B</u>	<u>Beta</u>	<u>Std. Error</u>	<u>t-value</u>	<u>Significance</u>
<i>Sensorimotor Skills</i>	4.80	.334	1.49	3.223	.002
<i>Attention/Executive</i>	3.16	.226	1.46	2.160	.034
<i>Memory/Learning</i>	5.56	.338	1.70	3.271	.002
<i>Visuospatial Abilities</i>	1.53	.129	1.29	1.184	.240

Table 5

Comparison of Performance on NEPSY Core Domains by Age Group (Covariate)

<u>Dependent Measure</u>	<u>Mean</u>	<u>Standard Deviation</u>
<i>Sensorimotor*</i>		
Under Age 5	20.04	6.41
Over Age 5	24.47	6.35
<i>Attention/Executive*</i>		
Under Age 5	23.96	6.68
Over Age 5	26.82	6.11
<i>Memory/Learning*</i>		
Under Age 5	24.73	7.91
Over Age 5	28.90	7.01
<i>Visuospatial Abilities</i>		
Under Age 5	15.87	4.88
Over Age 5	17.66	6.20

* $p < .05$

Table 6
Main Effects (Treatment Modality)

Treatment

Power= .258 (poor)

Test	Value	Exact F	Hypothesis DF	Error DF	Significance
Pillais Trace	.0482	1.026	4	81	.399

Roy-Bargman Stepdown F-tests

Variable	Stepdown F	DF	Hypothesis DF	Significance
<i>Sensorimotor Skills</i>	.148	1	84	.701
<i>Attention/Executive</i>	2.608	1	83	.110
<i>Memory/Learning</i>	.383	1	82	.537
<i>Visuospatial Abilities</i>	.983	1	81	.324

Table 7
Main Effects (Gender)

Gender

Power= .255 (poor)

Test	Value	Exact F	Hypothesis DF	Error DF	Significance
Pillais	.0629	1.361	4	81	.255

Roy-Bargman Stepdown F-tests

Variable	Stepdown F	DF	Hypothesis DF	Significance
<i>Sensorimotor Skills</i>	.038	1	84	.845
<i>Attention/Executive</i>	3.502	1	83	.065
<i>Memory/Learning</i>	.533	1	82	.467
<i>Visuospatial Abilities</i>	1.371	1	81	.245

Table 8

Correlation Coefficients Between Dependent and Independent Variables

	Age at Diagnosis	Age Tested	Gender	TX	Sens-motor SS	Atten/Exec SS	Mem/Learn SS	Visuospat SS
Age at diagnosis		.366**	-.108	-.121	.322**	.196	.308	.113
Age when tested	.366**		-.137	-.108	.248*	.197	.220*	.026
Gender	-.108	-.137		-.125	.014	-.125	-.087	.171
Treatment Type	-.121	-.108	-.125		.006	.160	-.041	-.047

Table 9
NEPSY Domain Scores by Age-Related Protocol
(3-4 year old protocol versus 5-12 protocol)

Test	Value	Exact F	Hypothesis DF	Error DF	Significance
Pillai's	.125	2.97	4	83	.024

Dependent Measure	Mean	Standard Deviation
<i>Sensorimotor*</i>		
Age 3-4 Version	19.64	1.02
Age 5-12 Version	24.87	1.07
<i>Attention/Executive*</i>		
Age 3-4 Version	23.62	1.01
Age 5-12 Version	27.18	1.07
<i>Memory/Learning*</i>		
Age 3-4 Version	24.73	1.20
Age 5-12 Version	28.90	1.27
<i>Visuospatial Abilities</i>		
Age 3-4 Version	15.82	0.89
Age 5-12 Version	17.71	0.94

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